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Effect of Non-Pulsatile Renal Blood Flow on Plasma Erythropoietin

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Erythropoietin is a hormone responsible for regulation of red blood cell production. Circulating erythropoietin values are regulated by renal oxygen supply, which is determined by hemoglobin concentration, hemoglobin oxygen saturation, and renal blood flow. Previous animal and human studies regarding erythropoietin regulation have assumed pulsatile renal blood flow. During cardiopulmonary bypass, non-pulsatile renal perfusion has been shown to result in decreased glomerular filtration rate and decreased renal blood flow in comparison to pulsatile perfusion. Repair of congenital heart disease during cardiopulmonary bypass is an attractive circumstance in which to study the effect of non-pulsatile blood flow on erythropoietin production. The hypothesis in this study was that non-pulsatile perfusion would result in increased erythropoietin production because of decreased renal oxygen supply. Fourteen children with congenital heart disease and without preoperative renal insufficiency or anemia were enrolled in the study. All patients underwent cardiopulmonary bypass with non-pulsatile flow. In addition, 10 control patients without congenital heart disease were enrolled. Six cardiopulmonary bypass patients had 1.5- to 6-fold increases in plasma erythropoietin concentrations from baseline. These patients had longer cardiopulmonary bypass times, more commonly performed under low flow deep hypothermic conditions. The remaining 8 patients with congenital heart disease, and all control patients, did not develop increased postoperative erythropoietin concentrations. The conditions under which cardiopulmonary bypass are performed appear to influence postoperative circulating erythropoietin concentrations. Am. J. Hematol. 57:144–147, 1998. © 1998 Wiley-Liss, Inc.

Key words: erythropoietin; renal blood flow; cardiopulmonary bypass

INTRODUCTION

Erythropoietin is a glycoprotein produced by a fibroblast-like renal interstitial cell, which is responsible for the regulation of red blood cell production [1]. Plasma erythropoietin values are regulated by renal oxygen supply. Tissue hypoxia has been proposed as the predominant stimulus for increased erythropoietin production [2]. Renal oxygen supply is determined by several factors including hemoglobin concentration, hemoglobin oxygen saturation, and renal blood flow. Renal blood flow can be characterized as pulsatile or non-pulsatile. Previous animal and human studies regarding erythropoietin regulation have assumed pulsatile renal blood flow. Information regarding the effects of non-pulsatile blood flow on renal function is limited. Non-pulsatile perfusion results in decreased glomerular filtration rate and decreased renal blood flow in comparison to pulsatile perfusion given equivalent perfusion pressures [3–5]. The reduction in renal blood flow is secondary to a preferential increase in systemic vascular resistance seen with non-pulsatile perfusion [3,4]. Non-pulsatile perfusion combined with hypothermia and hypotension are associated with increased release of renin, angiotensin II, antidiuretic hormone, and catecholamines when compared to pulsatile perfusion [6–9]. The increased activity of these mediators results in renal arteriolar vasoconstriction, reduced renal blood flow, and reduced renal parenchymal oxygenation [4]. Though these studies would imply a detrimental role for non-pulsatile renal blood flow, the superiority of pulsatile perfusion in preserving renal function has not been clearly demonstrated [10,11].

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Cardiopulmonary bypass utilizes non-pulsatile flow driven by roller pumps in the extracorporeal circuit. Repair of congenital heart disease under cardiopulmonary bypass represents an ideal condition to study the effect of non-pulsatile blood flow on erythropoietin production. The hypothesis in this study was that non-pulsatile perfusion would result in increased erythropoietin production because of decreased renal blood flow. To test this hypothesis, plasma erythropoietin values were measured in children before and after placement on non-pulsatile cardiopulmonary bypass for repair of congenital heart disease, and compared with age-matched control patients undergoing elective surgery.

MATERIALS AND METHODS

Patients

Fourteen children with congenital heart disease, and 10 healthy control children were enrolled in the study. No patient in the study had preoperative renal insufficiency or anemia. Preoperative renal insufficiency was defined as an elevated BUN or creatinine for age. Anemia was defined as a hemoglobin < 5th percentile for age.

Cardiopulmonary Bypass Group

All patients in this group underwent standard veno-arterial cardiopulmonary bypass. All cases were performed under moderate (25 to 32°C), or low flow deep (15 to 20°C) hypothermia. Patients who had cardiac surgery performed utilizing deep hypothermic circulatory arrest were not included in the study. Non-pulsatile flow was generated via a roller pump, and a membrane oxygenator and standard anesthetic regimen were used in all cases.

Control Group

All patients in this group underwent elective surgery for inguinal hernia or umbilical hernia repair.

Data and Sample Collection

Data consisting of demographic information and preoperative cardiac anatomy were collected and recorded. Preoperative and postoperative hemoglobin and serum creatinine values were recorded within 72 and 6 h of surgery, respectively. Erythropoietin concentrations were measured from the excess refrigerated plasma samples remaining in the laboratory after routine studies were performed within 72 h of surgery preoperatively and within 6 h of surgery postoperatively. Samples were stored at −70°C before performing the erythropoietin assays. The study was approved by the Institutional Review Board. Informed consent was waived because only routine laboratory values and otherwise discarded plasma samples were used in the study.

TABLE I. Preoperative and Postoperative Hemoglobin, Creatinine, and Erythropoietin in Cardiopulmonary Bypass Patients in Comparison to Control Patients†

	Cardiopulmonary bypass patients (n = 14)	Control patients (n = 10)
Preoperative Hb (g/dl)	13.2 ± 0.6	12.6 ± 0.5
Postoperative Hb (g/dl)	12.8 ± 0.3	12.1 ± 0.4
Preoperative creatinine (mg/dl)	0.6 ± 0.1	0.7 ± 0.1
Postoperative creatinine (mg/dl)	0.7 ± 0.2	0.6 ± 0.1
Preoperative Epo (mIU/ml)	9.6 ± 1.5	9.9 ± 1.1
Postoperative Epo (mIU/ml)	21.1 ± 4.6*	10.1 ± 0.8

†Hb, Hemoglobin; Epo, erythropoietin.
*$P < 0.05$ in comparison to control patient postoperative erythropoietin values and to cardiopulmonary bypass patients preoperative erythropoietin values.

Erythropoietin Assays

Plasma concentrations of erythropoietin were determined in duplicate by an enzyme-linked immunosorbent assay (Quantikine IVD, Research and Diagnostic Systems, Minneapolis, MN). Previously established plasma erythropoietin concentrations in healthy children range from 1.0 to 21.9 mIU/ml [12].

Data Analysis

Preoperative and postoperative continuous data was analyzed using the Student's *t*-test, and categorical data was analyzed using the Fisher Exact test. Results are expressed as mean ± SEM. A P value < 0.05 was considered significant.

RESULTS

Twenty-four patients (12 female) aged 42 ± 18 months were enrolled in the study. Underlying cardiac abnormalities in the 14 patients with congenital heart disease included atrioventricular canal (3), ventricular septal defect (3), atrial septal defect (2), truncus arteriosus (2), transposition of the great arteries (2), pulmonary stenosis (1), and partial anomalous pulmonary venous return (1). Cardiopulmonary bypass time was 87 ± 9 min (range 40 to 150 min), and aortic cross clamp time was 42 ± 6 min (range 18 to 100 min). Preoperative and postoperative hemoglobin, creatinine, and plasma erythropoietin values are shown in Table I. Mean postoperative plasma erythropoietin values were significantly higher than preoperative values for children undergoing cardiopulmonary bypass surgery. Mean postoperative plasma erythropoietin values were not different than preoperative values for controls. The mean time of postoperative erythropoietin sampling was 4.7 ± 1.6 h (range 2 to 7 h). Individual preoperative and postoperative erythropoietin values in the cardiopulmonary bypass patients are plotted in Figure 1.

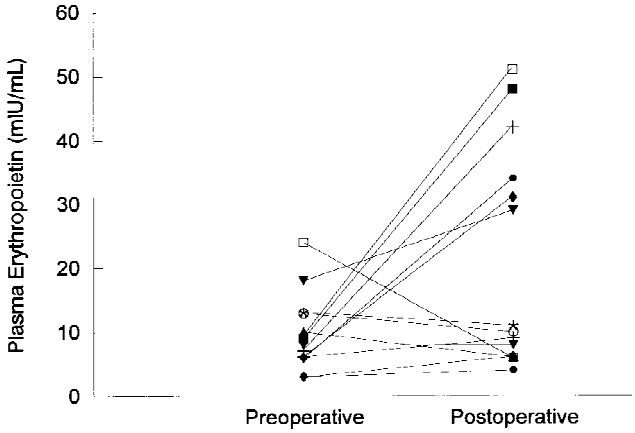

Fig. 1. Preoperative and postoperative plasma erythropoietin concentrations in individual children undergoing cardiopulminary bypass with non-pulsatile flow.

Six children undergoing cardiopulmonary bypass exhibited substantially higher postoperative erythropoietin values in comparison to baseline. The underlying diagnoses in these patients included transposition of the great arteries, truncus arteriosus, atrioventricular canal, and pulmonary stenosis. The characteristics of patients who had increased postoperative erythropoietin are compared to children who did not have increased postoperative erythropoietin in Table II. Bypass time and aortic cross clamp time were greater in patients with elevated postoperative erythropoietin levels; however, aortic cross clamp time did not reach statistical significance. A significantly greater number of patients with elevated postoperative erythropoietin levels underwent low flow deep hypothermic bypass.

TABLE II. Characteristics of Patients With and Without Elevated Postoperative Erythropoietin (Epo) Values*

	Elevated Epo (n = 6)	No elevated Epo (n = 8)	*P*
Preoperative Hb (g/dl)	13.3 ± 1.1	13.0 ± 0.6	0.83
Postoperative Hb (g/dl)	13.2 ± 0.5	12.3 ± 0.4	0.30
Preoperative Epo (mIU/ml)	9 ± 2	10 ± 2	0.79
Postoperative Epo (mIU/ml)	39 ± 4	8 ± 1	<0.001
Bypass time (min)	108 ± 12	71 ± 9	0.03
Aortic cross clamp time (min)	55 ± 10	32 ± 5	0.07
Low flow deep hypothermia	6 (100%)	2 (25%)	0.02

*Hb, hemoglobin; Epo, erythropoietin.

DISCUSSION

Control of erythropoietin production has been the subject of considerable investigation over the last decade. Circulating erythropoietin values are increased during conditions of reduced renal oxygen supply such as anemia [13,14], increased hemoglobin oxygen affinity [15], hypoxemia [16,17], and decreased renal blood flow [18–20]. These conditions stimulate erythropoietin production through the presentation of a hypoxic stimulus to a hypoxia-inducible cellular control element [21]. Decreased renal blood flow is unique among causes of diminished renal oxygen supply because it reflects renal ischemia, whereas anemia, increased hemoglobin oxygen affinity, and hypoxemia represent decreased renal oxygen supply secondary to renal hypoxemia. Reduced renal blood flow has been associated with increased erythropoietin production in patients with congestive heart failure [18], and in animals with renal artery constriction [19,20]. In these studies, though renal blood flow was decreased, the blood flow was pulsatile.

There have been few studies examining the impact of non-pulsatile blood flow on renal function. Several investigators have noted a decrease in both glomerular filtration rate and renal blood flow by as much as 30% during non-pulsatile blood flow when perfusion pressure is held constant [3–5]. Required flow rates in non-pulsatile bypass are greater than those in pulsatile bypass in order to maintain renal perfusion and avoid renal vein lactic acidosis [4]. The need for greater flow rates may be due to vasoconstriction of the glomerular arterioles and a progressive increase in renal vascular resistance, which has been noted during non-pulsatile perfusion [6]. Glomerular arteriolar vasoconstriction has been attributed to the vasoconstrictive effects of renin, angiotensin II, antidiuretic hormone, and catecholamines. The plasma levels of these mediators are increased in non-pulsatile in comparison to pulsatile renal perfusion [6–9]. Although these studies suggest that non-pulsatile blood flow is deleterious to the kidney, others have failed to demonstrate any advantage of pulsatile perfusion in the preservation of renal function following cardiopulmonary bypass [10,11,22–25].

The presumption in this study was that non-pulsatile cardiopulmonary bypass and the associated decreased renal perfusion would result in diminished renal oxygen supply. Furthermore, it was postulated that this state of renal hypoxemia would result in increased postoperative plasma erythropoietin values in comparison to the preoperative values. Six children with congenital heart disease in this study exhibited significantly higher postoperative than preoperative erythropoietin values. These children all underwent repair of complex congenital heart lesions under deep hypothermic low flow cardiopulmonary bypass with 66 to 150 min bypass times. These 6 patients had 1.5- to 6-fold increases in plasma erythropoietin concentrations from baseline. The remaining 8 patients with congenital heart disease in the study did not develop increased postoperative erythropoietin concentrations despite a mean cardiopulmonary bypass time of 71 min. There are several possible explanations for these findings. First, lower bypass flow rates combined with

deep hypothermia may have had a significant influence on upregulating erythropoietin production. All patients with elevated postoperative erythropoietin concentrations were repaired under low flow deep hypothermic conditions in comparison to only 2 of 8 patients who did not have elevated postoperative erythropoietin. Second, shorter duration cardiopulmonary bypass or aortic cross clamping may result in an inadequate hypoxemic stimulus to upregulate erythropoietin production. Children with elevated postoperative erythropoietin had longer mean bypass and aortic cross clamp times than those without elevated postoperative erythropoietin. Previous investigators have demonstrated elevated erythropoietin values within 2 h of a short exposure to hypoxia in humans, making this explanation less likely [16]. Finally, erythropoietin peaks may have been missed in some patients as a result of sampling error. All postoperative erythropoietin samples in this study were obtained within 6 h of surgery, with a mean time of 4.7 h. In a previous study, the half life of erythropoietin disappearance after hypoxia-induced endogenous erythropoietin overproduction in humans was 5.2 h. [16]. Elevated erythropoietin values in another study were no longer detectable 8 h after removal of a hypoxic stimulus [26].

CONCLUSIONS

In summary, exposure to non-pulsatile renal perfusion during cardiopulmonary bypass resulted in increased circulating erythropoietin values in 6 of 14 children. Control children undergoing elective surgery had no change in erythropoietin values after surgery. Circulating erythropoietin concentrations appear to be influenced by the conditions under which cardiopulmonary bypass is carried out, with longer cardiopulmonary bypass times and low flow deep hypothermia predisposing to higher erythropoietin levels. Further large-scale studies will need to be performed to further address these issues.

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